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EXAMINER	
CROUCH, D.	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on April 21,1995 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-15 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Applicant's arguments filed April 21, 1995 in paper no. 18 have been fully considered but they are not deemed to be persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification remains objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description for reasons presented in the previous office action. Claims 1-15 are drawn to a non-human transgenic mammal which secretes protein C into its milk, where the expression of the genomic protein C DNA sequences is regulated by the Sau3A-Kpn1 fragment of the mouse whey acidic promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process for producing said transgenic mammals and a process of producing protein C by isolation from the milk of the transgenic mammal. Therefore, DNA sequences which encode the mouse whey acidic promoter, protein C and protein C non-coding regions appear to be critical elements for the instant invention. A deposit of these DNA sequence is required for enablement.

Moreover, applicant is limited to transgenic mice where the transgene is human protein C DNA sequences contained in the Eco RI fragment of WAPpC1 and WAPpC2 regulated by the mouse whey acidic acid protein promoter, or where the transgene is the Sau3A-Kpn1

fragment of the mouse whey acidic promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process for producing said transgenic mice and a process of producing protein C by isolation from the milk of said transgenic mice. Applicant has not enable the production of all transgenic mammals which produce heterologous protein C in their milk. The production of transgenic mammals which exhibit tissue specific production of a specific protein is unpredictable. Applicant has not taught nor provided evidence that protein C DNA sequences will integrate into the genome of all mammals and that such integration will permit the production of heterologous protein C in the milk of all mammals.

Applicant argues that DNA sequences for practicing the invention may be obtained from a variety of sources. Applicant argues that WAP/protein C constructs prepared from these sources can be used to practice the instant invention. These arguments are not persuasive. The claims broadly encompass protein C DNA sequences from any animal with a mammary gland specific promoter from any mammal. Evidence is not of record that the disclosed method of isolating DNA sequences would permit the isolation of protein C sequences and mammary gland specific promoters from the collection of possibilities. The specific protein C sequence disclosed is human and the specific promoter is the mouse whey acidic protein promoter. Thus it would be unpredictable for the artisan to isolate protein C DNA sequences and mammary gland specific promoters from the divergent species that may contain them

without further guidance from the specification. In view of these considerations, the deposit requirement is deemed proper.

Applicant argues that they and the art have shown the production of several transgenic mammals which produce a desired protein using several mammary gland specific promoters. Applicant argues that this evidence provides sufficient grounds for a scope of "mammals" in the instant claims. These arguments are not persuasive. In a continuation of the response to applicant's arguments to the deposit requirement, applicant and the art have used in the majority of cases the same species mammary gland specific promoters and human protein C in the production of transgenic mammals. When the claims are read, applicant is including cross species promoter and protein C DNA sequence usage. Given that promoter activity is carefully regulated, it is unpredictable which species mammary gland promoters will be active is an unrelated species transgenic mammal. Likewise, given that human protein C must be β-carboxylated for activity, it is unpredictable that any given mammal will so modify protein C, either human or other species. It is recognized that applicant has disclosed transgenic pigs expressing human protein C from the mouse WAP promoter. This construct is only one example of the myriad of promoter-protein C combinations encompassed by the claims. The one example is insufficient to enable such a large group. In addition, mice and pigs are the mammals which have most frequently been used in transgenic technology. Thus to broadly claim "mammals" an expectation that all other mammals would be enabled by mice and pigs would need to be present. Thus the scope limitation to mice

and pigs is deemed proper.

Applicant argues that the limitation to a particular WAP/protein C encoding DNA sequence is improper because they have produce protein C with each construct disclosed in the specification. Applicant argues that the art teaches that a variety of protein C DNA sequences can be used to produce protein C in vitro. Applicant also argues that various methods for measuring protein C activity are disclosed in the specification, so that the activity of protein C produced in transgenic mammals can be detected. These arguments are not persuasive. Applicant has only shown the production of human protein C in the transgenic mice and pigs disclosed. Given the broad species encompassed by the claims, applicant is claiming protein C from all species. It would be undue experimentation to determine which protein C sequences would be properly β-carboxylated for activity in the various mammals encompassed by the claims. The cell culture data of record is all the expression of human protein C DNA sequences. Thus the scope limitation is deemed proper.

Claims 1-15 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification in the previous office action.

Claims 1-15 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record. Claims 1,3,6,11,12 and 14

contain the term "comprises substantially" or "substantially comprising" which is vague and indefinite as the reader can not be sure of other components of the promoter sequence. "Substantially" has no clear definition is the art and is open to broad interpretations. "Comprises" is open ended claim language. Thus the term "comprises substantially" or variations thereof, read as though the promoter sequence contains critical but unclaimed characteristics. In this regard the term is vague and indefinite by not defining the metes and bounds of the claims.

Applicant has referred to page 18, and has asked for clarification. At this citation, there is no definition of "substantially". The discussion at the citation describes only in general terms modifications that can be made to the sequence, but does not clear state what is encompassed by "substantially".

Claim 3 is vague and indefinite as the term "variant thereof" is not defined in the claim or specification. It can not be discerned if applicant means a structural or activity variant or some other type of variant.

Applicant has referred to pages 20-21 for a definition, and has asked for clarification. At the cited pages, there is a description of various ways to modify the WAP promoter, but no clear definition of "variants thereof". A variant of the WAP promoter, as claimed, does not have to have promoter activity.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102

of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-10 and 12-15 remain rejected under 35 U.S.C. § 103 as being unpatentable over Pittius et. al. (1988) Proced. Natl. Acad. Sci. 85, 5874-5878 in view of Grinnell et. al. (1987) Bio/Technology 5, 1189-1192, Brinster et al (1988) Proced. Natl. Acad. Sci. 85, 836-840, Campbell et al (1984) Nucl. Acids Res. 12, 8686-8697 and Clark et al (1987) TIBTECH 5, 20-24 for reasons of record. Pittius teaches that tPA can be detected in the milk of a transgenic mouse, when expression of the tPA transgene is regulated by the mouse whey acidic protein promoter and the tPA transgene contains a signal peptide which directs secretion of the protein product into the milk (page 5875, col. 3, parag. 1, line 1 to page 5876, col. 2, through parag. 2 and page 5876, fig. 2). Grinnell teaches the expression of human protein C in tissue culture cells transfected with an expression vector comprised of the cDNA for human protein C and regulatory sequences, where active protein C was isolated from the culture media (page 1191, col. 2, parag. 1). Brinster teaches that the inclusion of intron sequences enhances the expression of a transgene in transgenic mice (see abstract and page 837, fig. 1). Campbell teaches the genomic sequence for mouse

protein C (see pages 8691-8692, fig. 3). Clark teaches the production of compounds of pharmaceutical importance in transgenic mammals by the specific expression of DNA sequences which encode a compound of interest in the mammary gland of the transgenic mammal, the secretion of the compound into the milk of the mammal and the subsequent isolation of the compound from the milk (page 22, col. 1, parag. 2 to col. 2, line 13).

Applicant argues that the transgenic animals have an unexpected result of great tissue specificity and improved expression of protein C in their milk. Applicant argues that the art does not teach the long WAP promoter or any specific genomic DNA to choose. Applicant argues that protein C is complex protein that must undergo unusual modifications. Applicant argues that t-PA does not undergo these modifications and can not provide a reasonable expectation of success in producing protein C. Applicant also argues that mammary cells in culture produce very low amounts of active protein C and therefore it would not have been expected that active protein C could be made in mammary glands. These arguments are not persuasive. The claims are not drawn to a transgenic mammal which expresses a DNA sequence encoding protein C, but rather to a transgenic mammal which expresses a protein having protein C activity. Thus the t-PA reference is applicable as it has protein C activity. Protein C binds to its substrate and is proteolytic. These same activities are possessed by protein C. Thus t-PA has protein C activity. Thus the artisan would have been motivated and provided a reasonable expectation of success to produce any protein that binds its substrate or is proteolytic, as

examples, in view of the cited prior art. Further, Grinnell states that some active protein C was produced. Thus for those claims without activity or concentration limitations, the artisan would have been motivated to produce transgenic mammals expressing some level of active protein C. Applicant has not provided evidence that ell culture data reflects the transgenic mammal situation, or that a low level of production would have deterred the artisan away. Cell culture data may not necessarily reflect the transgenic situation. Thus given the teachings of Grinnell that any amount of protein C is produced would have motivated the artisan to produce transgenic mammals expressing protein C in their milk.

Claim 11 remains rejected under 35 U.S.C. § 103 as being unpatentable over Colpan et.al. (1984) Journal of Chromatography 296, 339-353 in view of Hogan et. al. (1986) Manipulation of the Mouse Embryo, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. pages 153-203 for reasons of record. Colpan teaches the purification of plasmid DNA by anion exchange HPLC. Hogan states that DNA for the production of transgenic animals must free of contaminants which may harm the egg.

Applicant argues that Hogan published after Colpan does not teach DNA purification by the method of Colpan. Applicant further argues that there is no motivation in Colpan to purify DNA for the making of transgenic animals. These arguments are not persuasive. Hogan in teaching that DNA to be used in transgenic animal production is sufficient motivation to use any method known in the art for purifying DNA. Colpan discusses the purification of plasmid DNA and DNA fragments, as well as other nucleic acids, by HPLC

(page 348, parag. 2 to page 351, line 4). Colpan states that the purification by HPLC would be less time consuming and therefore helpful to the artisan. The dates of publication of references are only relevant to the filing date of the specification, and are not relevant to each other. Given the cited prior art, the particular DNA to be purified is obvious absent results to the contrary.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.